To:

From the INTERNATIONAL BUREAU

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE

COMMUNICATION OF THE INTEL APPLICATION (TO DESIGNATE WHICH APPLY THE 30 MONT LIMIT UNDER ARTICLE 2 (PCT Rule 47.1(c))	D OFFICES TH TIME	Sternwartstr. 4 81679 München Patentanwille ALLEMAGNE Reitstötter, Kinzebach & Part.	
Date of mailing (day/month/year) 24 November 2005 (24.11.2005)		Eing	3 0. Nov. 2005 Cod
Applicant's or agent's file reference M/45173-PCT		IMPORTANT NOTICE	
International application No. PCT/EP2004/008207	International filing dat 22 July 2004	te (day/month/year) 4 (22.07.2004)	Priority date (day/month/year) 24 July 2003 (24.07.2003)
Applicant	FERRER INTERNA	ACIONAL, S.A. et al	

- ATTENTION: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below: 17 February 2005 (17.02.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SG, SK, SL, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit). Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Ellen Moyse

Facsimile No.+41 22 338 89 75

Form PCT/IB/308(Second and Supplementary Notice) (January 2004)

Facsimile No.+41 22 740 14 35

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

REITSTÖTTER, KINZEBACH & PARTNER (GBR)

SternwartstRæitstötter, Kinzebach & Part. 81679 München

Germany

Eing. 14. Ukt. 2004

Sternwartstr. 4 D-81679 München

Date of mailing (day/month/year) 28 September 2004 (28.09.2004)	IMPORTANT NOTIFICATION	
Applicant's or agent's file reference	International application No.	
M/45173-PCT	PCT/EP2004/008207 ~	

The applicant is hereby **notified** that the international Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

FERRER INTERNACIONAL, S.A. (for all designated States except US)
ANGLADA, Luis et al (for US)

International filing date

22 July 2004 (22.07.2004) 🗸

Priority date(s) claimed

24 July 2003 (24.07.2003) 12 July 2004 (12.07.2004)

Date of receipt of the record copy

by the International Bureau

10 August 2004 (10.08.2004)

List of designated Offices

AP:BW,GH,GM,KE,LS,MW,MZ,NA,SD,SL,SZ,TZ,UG,ZM,ZW

EA:AM,AZ,BY,KG,KZ,MD,RU,TJ,TM

EP:AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PL,PT,RO,SE,SI,SK,

TR

OA:BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG

National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BW,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,

DZ,EC,EE,EG,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,

LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NA,NI,NO,NZ,OM,PG,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,

SL,SY,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer:

S. GROBET

Telephone No. (41-22) 338 8018

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

	Date of mailing (day/month/year) 28 September 2004 (28.09.2004)	IMPORTANT NOTIFICATION
۔	Applicant's or agent's file reference M/45173-PCT	International application No. PCT/EP2004/008207

ATTENTION

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The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

X time limits for entry into the national phase - see updated important information (as of April 2002)

| X | requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at http://www.wipo.int/pct/en/index.html.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

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NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year)

То:	
REITSTÖTTER, KINZEBACH & PARTNER (GBR) Sternwartstr. Reitstötter, Kinzebach & Part. 81679 München Eing 03. Dez. 2004 Sternwartstr. 4 0-81679 München	
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From the INTERNATIONAL BUREAU

25 November 2004 (25.11.2004)	The state of the s		
Applicant's or agent's file reference M/45173-PCT	IMPORTANT NOTIFICATION		
International application No. PCT/EP2004/008207	International filing date (day/month/year) 22 July 2004 (22.07.2004)		
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 July 2003 (24.07.2003)		

Applicant

FERRER INTERNACIONAL, S.A. et al

- 1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 3. (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
24 July 2003 (24.07.2003) 🥣 12 July 2004 (12.07.2004) 😊			09 Nove 2004 (09.11.2004) 09 Nove 2004 (09.11.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Aurora CENDANA (Fax: 338 89 75)
Facsimile No. (41-22) 338.89.75	Telephone No. (41-22) 338 9905

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file M/45173-PCT	e reference	FOR FURTHER A	ACTION	See Form PCT/IPEA/416	
International application No. International filing date PCT/EP2004/008207 22.07.2004			(day/month/year)	Priority date (day/month/year) 24.07.2003	
International Patent Cla C07D487/04, A61K	• •	ational classification and 22	IPC		
Applicant FERRER INTERNA	ACIONAL S.A. et	al.			
This report is the Authority under	e international pre Article 35 and trar	liminary examination r	eport, established by t nt according to Article	his International Preliminary Examining 36.	
2. This REPORT	consists of a total o	of 7 sheets, including	this cover sheet.		
This report is al	so accompanied b	y ANNEXES, comprisi	ing:		
a. 🗆 sent to t	he applicant and to	the International Bure	eau) a total of sheets	, as follows:	
and/		ng rectifications author		amended and are the basis of this report see Rule 70.16 and Section 607 of the	
beyo					
sequenc	e listing and/or tabl	ureau only) a total of (i les related thereto, in o Listing (see Section 80	computer readable for	per of electronic carrier(s)) , containing a m only, as indicated in the Supplemental e Instructions).	
4. This report cont	ains indications rel	ating to the following i	tems:		
☑ Box No. I	Basis of the opin	ion			
☐ Box No. II	Priority				
Box No. III	Non-establishme	ent of opinion with rega	ard to novelty, inventiv	e step and industrial applicability	
☐ Box No. IV	Lack of unity of in				
⊠ Box No. V	applicability; cita	tions and explanations	 with regard to novel supporting such state 	ty, inventive step or industrial ement	
☐ Box No. VI	Certain documer		N . A'		
☐ Box No. VII		n the international app ions on the internation			
□ BOX NO. VIII	Certain observat	ions on the internation	ai application		
Date of submission of the demand		Date of completion of t	his report		
05.01.2005			24.06.2005		
Name and mailing addre	ss of the internationa	<u> </u>	Authorized Officer		
preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465			Wörth, C Telephone No. +49 89	2399-8726	

80/563104(AP29 Res'd FCT/PTO 30 DEC 2005

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/008207

•			
	Вс	x No. I Ba	is of the report
*1.	Wi file	th regard to t d, unless oth	e language , this report is based on the international application in the language in which it was
		This report which is the	s based on translations from the original language into the following language , language of a translation furnished for the purposes of:
		☐ publicat	onal search (under Rules 12.3 and 23.1(b)) on of the international application (under Rule 12.4) onal preliminary examination (under Rules 55.2 and/or 55.3)
2.	ha	ve been furni	e elements* of the international application, this report is based on (replacement sheets which hed to the receiving Office in response to an invitation under Article 14 are referred to in this ally filed" and are not annexed to this report):
	Des	scription, Pag	es es
	1-5	5	as originally filed
	Cla	ims, Number	
	1-3	3	as originally filed
		a sequence	isting and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3.			nents have resulted in the cancellation of:
		☐ the desc	iption, pages s. Nos.
		☐ the draw	ngs, sheets/figs
		any table	ence listing (specify): (s) related to sequence listing (specify):
4.	had	not been ma	as been established as if (some of) the amendments annexed to this report and listed below de, since they have been considered to go beyond the disclosure as filed, as indicated in the x (Rule 70.2(c)).
		☐ the desc☐ the claim☐ the draw	
		☐ the sequ	nce listing (specify): s) related to sequence listing (specify):
	*	If item 4	applies, some or all of these sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/008207

	ox No. III Non-establishment oplicability	of op	oinion with regard to novelty, inventive step and industrial
			ention appears to be novel, to involve an inventive step (to be non- have not been examined in respect of:
	the entire international applica	tion,	
×	claims Nos. 22-32 with respec	t to IA	4
	because:		
×	the said international application subject matter which does not	on, or requi	the said claims Nos. 22-32 with respect to IA relate to the following ire an international preliminary examination (specify):
	see separate sheet		
	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):		
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.		
	no international search report has been established for the said claims Nos.		
	the nucleotide and/or amino ac C of the Administrative Instruc		quence listing does not comply with the standard provided for in Annex in that:
	the written form		has not been furnished
			does not comply with the standard
	the computer readable form		has not been furnished
			does not comply with the standard
			and/or amino acid sequence listing, if in computer readable form only, do ements provided for in Annex C-bis of the Administrative Instructions.
	See separate sheet for further	detai	ls

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/EP2004/008207

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

1-36

No: Claims

Inventive step (IS)

Yes: Claims

1-36

No:

o: Claims

Industrial applicability (IA)

Yes: Claims

No: Claims

Yes: 1-21,33-36

2. Citations and explanations (Rule 70.7):

see separate sheet

IAP20 REC'S FOR FTO 30 DEC 2005

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/EP2004/008207

1. Re Item I (Basis of the report)

Reference is made to the following documents:

- D1: EP-A-0 264 773 (AMERICAN CYANAMID CO) 27 April 1988 (1988-04-27)
- D2: US-A-5 538 977 (DUSZA JOHN P ET AL) 23 July 1996 (1996-07-23)
- D3: DE 43 33 705 A (EGE GUENTER PROF DR) 6 April 1995 (1995-04-06)
- D4: GB-A-1 412 017 (ICN PHARMACEUTICALS) 29 October 1975 (1975-10-29)
- D5: DE 101 53 344 A (GRUENENTHAL GMBH; UNIVERSITEIT LEIDEN LEIDEN (NL)) 15 May 2003 (2003-05-15)
- D6: WO 00/59908 A (DU PONT PHARM CO) 12 October 2000 (2000-10-12)

2. Re Item III (Non-establishment of opinion with regard to novelty, inventive step and industrial applicability)

Claims 22-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3. Re Item V (Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement)

3.1 Subject-matter

The present application relates to certain pyrazolo[1,5-a]pyrimidines characterized by a nitro-group at position 3. The claimed compounds exhibit affinity for GABAα receptor thereby being useful for the treatment of inter alia anxiety and sleep disorders.

3.2 Novelty

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The subject-matter of claim 1 differs from

-D1-D3 in view of the present **nitro-group** at position 3 of the pyrazolo[1,5-

a]pyrimidine moiety

- D4 in view of present R₁ being an aromatic moiety (see definition of corresponding R₂ in D4)
- D5-D6 in view of the present **nitro-group** at position 3 of the pyrazolo[1,5-a]pyrimidine moiety.

The requirements of Art. 33(2) PCT are fulfilled.

3.3 Inventive step

Document D2 is considered as closest prior art. This document discloses pyrazolo[1,5-a]pyrimidines substituted at position 3 and 7 having anxiolytic, anti-convulsant, sedative-hypnotic and skeletal relaxant activity.

In view of this document, the problem to be solved can be regarded as the provision of further compounds having the same activity.

The solution provided consists in compounds according to present claim 1 characterized by a nitro-group at position 3 of the pyrazolo[1,5-a]pyrimidine core.

The problem is considered as being solved in view of the pharmacological data on pages 17-21 of the specification.

The provided solution is presently considered as involving an inventive step. Although documents D1-D3 already disclose a variety of suitable substituents (from hydrogen to aromatic substituents) at position 3 of the pyrazolo[1,5-a]pyrimidine core, the comparative tests vis-à-vis zaleplon, which differs only in the substituent at position 3, indicate a surprisingly superior activity of the claimed compounds.

The requirements of Art. 33(3) PCT are fulfilled.

3.4 Industrial applicability

For the assessment of the present claims 25-32 on the question whether they are

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/EP2004/008207

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3.5 Certain observations

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As far as the subject-matter of claims 22-24, 34 and 35 is concerned it is stressed that the selective occupation of a receptor cannot be considered in itself as a therapeutic application. The discovery, that a substance binds a receptor still needs to find an (unexpected) practical application in the form of a defined real treatment of any pathological condition to be considered as an invention eligible for patent protection.